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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/418,095	10/14/1999	JOHN A. COPLAND III	UTMB/GAL:239	8391

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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 01/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/418,095	Applicant(s) COPLAND III ET AL.	
	Examiner Stuart Baum	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-46 are pending in the present application and they are examined on the merits herein.

Upon further consideration of the prior art, the suspension letter dated 04/10/01 in Paper No. 8 is vacated.

Responses to amendment

The prior art rejections in the previous Office Action in Paper No. 7 are withdrawn in light of the Declaration of Applicants under 37 C.F.R. 1.131.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Upon careful reconsideration of this application, following is a new ground of rejection.

Claim Rejections - 35 USC § 112

Claim 32 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction

or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claim is directed to a method for inhibiting the growth of a cancer cell comprising (i) contacting the cancer cell with a thiazolidinedione compound; and (ii) contacting the cancer cell with a chemotherapeutic drug or irradiating the cancer cell with X-ray irradiation, UV-irradiation, γ-irradiation, or microwaves, in amounts effective to inhibit the growth of the cancer cell, wherein the thiazolidinedione compound is contacted with a cancer cell by administering the thaizaolidinedione regionally, endoscopically, intravenously, intralesionally, percutaneously, subcutaneously, intraperitoneally, intratracheally, intramuscularly, or by perfusion, and wherein further comprising contacting the cell with a therapeutic polynucleotide selected from the group consisisting of a Dp gene, p21, p16, p27, E2F, Rb, APC, DC, NF-1, WT-1, MEN-1, MEN-11, BRCA1, VHL, FCC, MCC, ras, myc, neu, raf, erb, src, fms, jun, trk, ret, gsp, hst, bcl, abl, Bax, Bcl-Xs and E1A, wherein the therapeutic polynucleotide is expressed in the cell.

The specification teaches a method utilizing troglitazone or other thiazolidinedione compounds such as pioglitazone, rosiglitazone either alone or in combination with other chemotherapeutic agents known in the art to treat cancer. Specifically, the specification discloses that osteosarcoma Saos-2 cells contain functional PPAR-gamma and upon exposing the cells to troglitazone, osteosarcoma cell

proliferation measured by total DNA content and thymidine incorporation is inhibited. The specification further teaches that troglitazone is effective in lowering the doses of 5-fluorouracil (5-FU) and doxorubicin required for inhibiting the proliferation of Saos-2 cells. Among the thiazolidinedione compounds tested in this cell culture system, troglitazone is shown to be superior to pioglitazone and rosiglitazone (BRL 49653) in its ability to inhibit cell proliferation. Similar inhibition effects of troglitazone, pioglitazone and rosiglitazone on cell proliferation of human renal URMC 3, 6 and 7 tumor cells were observed. Various human ovarian cancer cell lines including CaOV3, 222, PA-1, 2774, OV CAR3 and SK OV3 were also tested for the proliferation inhibitory effects of the thiazolinedione compounds. The data suggested that responsiveness of individual thiazolidinedione could not be predicted in these ovarian cell lines. Furthermore, in a combined application of taxol and troglitazone to isolated human ovarian tumor cells, an enhanced inhibitory activity over that of either agent used alone was obtained, however this enhanced inhibitory effect is significantly less than that obtained for the commonly used regimen of taxol and cisplastin already known in the art.

The above evidence has been noted and considered. However, it can not be reasonably extrapolated to the instant claimed invention. The nature of claim 32 would fall within the realm of *in vivo* gene therapy. At the effective filing date of the present application, the art of gene therapy was highly unpredictable regarding to obtaining desired therapeutic effects. In a meeting report on gene therapy and translational cancer research, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) stated that "This workshop reviewed some recent advances in gene delivery, gene expression, immune

manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement to make gene therapy a reality" (page 471, col. 1, last sentence of first full paragraph). There are several factors known to limit the effectiveness of gene therapy, these include, the lack of optimal vectors, the lack of stable *in vivo* transgene expression, the adverse host immune responses to the vectors, and most importantly the lack of an efficient gene delivery to target tissues (page 474, col. 2, last paragraph). The instant specification fails to provide any relevant information regarding to the specific vectors used, the effective dosage of the vectors utilized, the route and frequency of administering these vectors to cancer cells such that effective amounts of encoded polypeptides listed in the claim could be expressed to yield the desired therapeutic effects. There is no evidence of record indicating or suggesting any of the recited therapeutic polynucleotide could be expressed at an effective amount in cancer cells to yield any therapeutic effects, let alone any additional or synergistic therapeutic effects to be attained in combination with a thiazolidinedione compound and a chemotherapeutic drug or irradiation. Particularly, for inhibiting the growth of a variety of cancer cell types contemplated by Applicants. The CAFC has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court also stated that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genetech, Inc. v. Novo Nordisk A/S*, 42 USPQ 2d 1001, at 1005).

Regarding to the breadth of the instant claim encompassing a laundry list of therapeutic polynucelotides, it should be noted that additional factors such as the level of mRNA produced, the stability of the protein produced, the protein's proper compartmentalization within the cell differ dramatically based on which protein being produced, and therefore the desirable therapeutic effects sought to achieve (Eck & Wilson, Gene-based therapy, 1996, column 2 page 81 continues to page 82). With the level of transgene expression, its duration, and its *in vivo* therapeutic effects are not always predictable, coupled with the lack of guidance provided by the present disclosure, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

The instant claim also encompasses any route of administering a therapeutic polynucleotide *in vivo* to contact the cancer cell. Vector targeting *in vivo* to desired cells or organs continues to be unpredictable and inefficient. This is supported by numerous teachings in the art. For example, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that "Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated that one of the main obstacles hampering a successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time." (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art which show promises. One of which is the

ligand-targeted receptor-mediated vector approach with a relatively higher level of tissue specificity than viruses can offer. However, this approach to gene therapy is much less efficient than viral gene delivery (column 1, last paragraph, page 65). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy, and the problems which are associated with each. They also indicated clearly that resolution to vector targeting had not been achieved in the art at about the effective filing date of the present application (see the entire article). Verma & Somia discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that an efficient expression is not achieved (see page 239, and second and third columns of page 242). Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type." (page 240, sentence bridging columns 2 and 3). The instant specification fails to teach one of skill in the art how to overcome the unpredictability for *in vivo* vector targeting such that an efficient transfer and expression of a recited therapeutic polynucleotide could be achieved by any mode of gene delivery to yield the therapeutic effects contemplated by Applicants.

Accordingly, due to the lack of guidance provided by the instant specification regarding to the issues set forth above, the unpredictability of the gene therapy art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, 9, 10, 13, 27, 31-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5, 6, 9, 10, 13, 27, 31 and 32 recite the limitation "the cell" in the claims. There is insufficient antecedent basis for this limitation in the claim. In claim 1 from which these claims are dependent upon, "a cancer cell" is recited not "a cell".

In claim 33, it is unclear what is encompassed by the phrase "to inhibit the cancer". Inhibit the growth, metastasis or which aspects of the cancer? The metes and bounds of the claim can not be clearly determined.

Claim Rejections - 35 USC § 102

Claims 1-8, 16-23, 28, 30, 33-35 and 40-41 are rejected under 35 U.S.C. 102(e) as being anticipated by Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997) as evidenced by Medenica et al. (U.S. Patent No. 5,736,129), Knight et al. (U.S. Patent No. 6,090,407) and Roth et al. (U.S. Patent No. 5,747,469).

Urban et al. teach that troglitazone and related thiazolidinedione compounds (including pioglitazone and BRL49653, see example 1) can be used in the treatment of the climacteric and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione

derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma, rhabdomyosarcomas, fibrosarcomas, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated that "Use of troglitazone therapy in conjunction with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27). Although Urban et al. do not teach specifically the chemotherapeutic drugs or types of radiation used in combination with the troglitazone therapy, however the types of chemotherapeutic drugs and the types of radiation utilized in the treatment of cancer are well known in the art as evidenced by the teachings of Medicina et al., Knight et al., and Roth et al. Medenica et al. disclosed treating cancer cells by the use a multidrug chemotherapeutic regiment. The utilized drugs that are taught in the issued patent encompass alkylating agents such as Cis-platin, cyclophosphamide; mitotic inhibitors such as etoposide or VP-16, taxol, vinblastine; antibiotics such as doxorubicin, dactinomycin; an antimetabolite such as 5-FU and a corticosteroid hormone such as prednisone (See columns 6-10). Knight et al. the use of anti-cancer drugs including a nitrosourea agent such as lomustine, and others such as taxol, 5-FU, etoposide... for treating cancer (See claim 1 on column 16). Roth et al. teach killing cancerous cells

using a tumor suppressor gene, p53 in a recombinant retrovirus, in combination with a DNA damaging agent. An embodiment of the invention disclosed by Roth et al. involves the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent in combination with p53 gene transfer to treat cancer (column 8, second paragraph and see claims 51 and 61-67). Roth et al. further noted that a combination treatment is required to prevent local recurrence following primary tumor resection (See column 3, lines 20-25).

Accordingly, Urban et al. anticipate the instant claimed invention.

Claim Rejections - 35 USC § 103

Claims 1-31 and 33-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tontonoz et al. (Proc. Natl. Acad. Sci. 94:237-241, 1997; IDS) in view of Urban et al. (U.S. Patent No. 5,814,647 with the effective filing date of 3/4/1997), Medenica et al. (U.S. Patent No. 5,736,129), Knight et al. (U.S. Patent No. 6,090,407) and Roth et al. (U.S. Patent No. 5,747,469).

Tontonoz et al. disclose that thiazolidinedione compound such as pioglitazone, troglitazone and BRL49653 (rosiglitazone) can induce terminal differentiation of human liposarcoma cells *in vitro*, and that thiazolidinedione-induced differentiation of liposarcoma cells is accompanied by cell cycle growth arrest, which is in effect inhibiting liposarcoma cell growth (see the entire article, particularly page 240, col. 1). Tontonoz et al. further teach that thiazolidinedione compounds, at least for pioglitazone and BRL49653, have additive effects on terminal differentiation of human liposarcoma cells

with an RXR-specific ligand LG268. Moreover, on the basis of their data, Tontonoz et al. suggested that thiazolidinedione compounds and RXR-specific retinoids can be used to stimulate differentiation and growth arrest of human tumors *in vivo* (page 241, col. 1, second full paragraph). Tontonoz et al. do not teach contacting the cancer cells with a chemotherapeutic drug or irradiating the cancer cell with X-ray irradiation, UV-irradiation, γ-irradiation or microwaves in combination with a thiazolidinedione compound, or specific cancer cell types recited in dependent claims or specific steps in certain methods claimed.

Urban et al. teach that troglitazone and related thiazolidinedione compounds can be used in the treatment of the climacteric and cancer. Specifically, Urban et al. disclose that therapeutic levels of troglitazone can kill rapidly growing cancerous cells expressing the orphan nuclear receptor PPARγ, while not affecting the viability of normal cells (col. 3, lines 1-9). A type of cancer that is likely to be treated with troglitazone and related thiazolidinedione derivatives are mesenchymal tumors including but not limited to sarcomas, congenital mesoblastic nephroma, rhabdomyosarcomas, fibrosarcomas, hemangiopericytoma and mesotheliomas (col. 3, lines 13-22). Urban et al. also stated that "Use of troglitazone therapy in conjunction with other chemotherapeutic agents, radiation, or surgery may in many cases be the preferred mode of treatment. Troglitazone treatment therefore, would inhibit the growth of the cancer so that other therapies may be added, thereby increasing the likelihood of curing the patient. Troglitazone and related thiazolidinedione derivatives may additionally be used to treat patients with severely metastatic disease. Such treatment may slow tumor

growth and reduce tumor mass, thereby prolonging survival and increasing the quality of terminal cancer patients" (col. 24, lines 17-27).

Medenica et al. disclosed a method of treating cancer cells by the use a multidrug chemotherapeutic regiment. The utilized drugs that are taught in the issued patent encompass alkylating agents such as Cis-platin, cyclophosphamide; mitotic inhibitors such as etoposide or VP-16, taxol, vinblastine; antibiotics such as doxorubicin, dactinomycin; an antimetabolite such as 5-FU and a corticosteroid hormone such as prednisone (See columns 6-10). Knight et al. taught a method of delivering anti-cancer drugs including a nitrosourea agent such as lomustine, and others such as taxol, 5-FU, etoposide... in treating cancer (See claim 1 on column 16). Roth et al. disclosed a method of killing cancerous cells using a tumor suppressor gene, p53 in a recombinant retrovirus, in combination with a DNA damaging agent. An embodiment of the invention disclosed by Roth et al. involves the use of gamma-irradiation, X-rays, UV-irradiation or microwaves as a DNA damaging agent in combination with p53 gene transfer to treat cancer (column 8, second paragraph and see claims 51 and 61-67). Roth et al. further noted that a combination treatment is required to prevent local recurrence following primary tumor resection (See column 3, lines 20-25).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method disclosed by Tontonoz et al. by combining the use of a thiazolidinedione compound (e.g., troglitazone, pioglitazone and rosiglitazone) in conjunction with other chemotherapeutic agents, radiation, or surgery to inhibit the growth or killing liposarcoma cells or mesenchymal tumor cells or tumor

cells expressing PPARγ in both *in vitro* and *in vivo* as taught by Urban et al. With respect to the effectiveness of thiazolidinedione in inhibiting the growth of a wide range of tumor cells, in the absence of the evidence to the contrary, the growth of recited tumor or cancer cells is also inhibited by thiazolidinedione. Therefore, it would have been obvious for one of ordinary skill to test the growth inhibitory effects of a thiazolidinedione compound to any known cancer cell lines or any cancer tissues and the use of a thiazolidinedione as an anti-cancer therapy in conjunction with other chemotherapeutic agents, radiation, or surgery. It is noted that although specific chemotherapeutic drugs and/or specific method steps involved in the combined therapies (thiazolidinedione with either chemotherapy or irradiation or surgery) are not taught in both Tontonoz et al. and Urban et al., at the effective filing date of the present application it is within the scope of skill of an ordinary skilled artisan to modify and carry out such recited limitations because the art on chemotherapy, irradiation and surgery for treating cancer is well known. This is exemplified by the teachings of Medicina et al., Knight et al., and Roth et al. as presented above. One of ordinary skill would have been motivated to carry out the above modification because it is apparent that a thiazoldinedione compound is useful in adjuvant therapy for cancer treatment due to its antiproliferative effects and its low toxicity and well tolerance in humans (thiazoldidinedione compounds are well known antidiabetic drugs). Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 308-0009.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER